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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,303	07/18/2003	Hsing-Wen Sung	S&T-109	7283

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,303	SUNG ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/25/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,15,16,19 and 21-24* is/are pending in the application.

4a) Of the above claim(s) *1-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,15-17,19 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07/18/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, without traverse, with the Group II is acknowledged. Claims 1-11 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims.

2. Claims 12, 15-17, 19 and 21-24 are currently pending for prosecution on the merits.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Priority

4. According to the Bib Data Sheet, this application is a CIP of 09/297,808 filed 09/27/2001, matured into USP 6608040 which is a 371 of PCT/US97/20113 filed 110/04/1997 which claims benefit of 60/030701 filed 11/05/1996. This application also claims benefit of 60/398003 filed 07/232002.

While a method for administering a microsphere composition comprising heparin and gelatin crosslinked with genipin was disclosed in 60/398003, said composition was not disclosed in the US Serial No. 09/297808 nor 60/030701. Therefore, the present application has an effective filing date of 07/23/2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 12, 15-17, 19 and 21-24 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses genipin as a suitable example of bioactive agent, which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, the claims 12, 15-17, 19 and 21-24 are directed to encompass "derivatives" and/or "analogs" which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these meet the written description provision of 35 USC 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompasses a myriad of possibilities. To the extent that no structure function data is disclosed in connection with theses functionally described compounds to correlate, or there is not disclosed correlation established between these functional drugs and the contemplated desired therapeutic effect to be achieved in practicing the instant invention, the specification provides insufficient written description to support the genus encompassed by the claims.

Vas-Cath Inc. Mahurkar, 19 USPQ2d 1111, makes clear the "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of genipin, the skilled artisan cannot envision the detailed chemical structure of the encompassed derivatives, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966(1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)* ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures,

diagrams, formulas, etc., that set forth the claimed invention." *Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.*

6. Claims 12, 15-17, 19 and 21-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "therapeutic treatment of restenosis or reduction of intimal smooth muscle cell proliferation following angioplasty", does not reasonably provide enablement for the term "therapeutic treatment". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The inventions relate to a method of administration of a pharmaceutical microsphere comprising a bioactive agent consisting of heparin and gelatin carrier wherein the gelatin carrier is crosslinked with genipin, its analog or derivatives thereof to the patient for the therapeutic treatment.

There are no known compounds of similar structure which have been demonstrated to treat or diseases or conditions. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of pharmacology.

The relative skill of those in the art of pharmaceuticals and unpredictability of pharmaceutical art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for the therapeutic treatment encompassed by the instant claim. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The instant claims embrace therapeutic treatment of any diseases or conditions. The instant claims cover "diseases or conditions" that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmacy art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the preventive utility of the instant compounds.

The specification discloses that crosslinking of collagen material such as gelatin with genipin increases biodurability and reduces antigenicity and immongenicity (pages 1-2, para. [0003]), and suggests that the incorporation of anti-thrombogenic agent such as heparin in combination of gelatin crossed linked with genipin to the medical device such as stent would be

useful in the treatment of restenosis followed by angioplasty (page 3, para. [0010] and page 43, para. [0185]). However, there is no demonstrated correlation that the tests and results apply to the claimed therapeutic utility embraced by the instant claims.

Since the efficacy of the claimed compound(s) in treating any diseases or conditions mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 12, 15-17, 19 and 21-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites "consisted of". It is not clear whether "consisted of" is used as closed transitional language. Proper closed transitional phrase is "consisting of ", not "consisted of". Such discrepancy leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

For the examination purpose, the term "consisted of" is interpreted as "consisting of".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 12, 15-17, 19 and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (WO 98/19718) in view of Pinchuk et al. (US 6545097), and further in view of Tsai et al. (Biomaterials 22, 2001, 523-533), Royer (USP 5783214) and Gagnieu et al. (USP 5763579).

The claims are drawn to a method of administering a pharmaceutical microsphere composition comprising heparin and gelatin carrier crosslinked with genipin to a body of patient for the therapeutic treatment. Further limitations include "a step of loading said pharmaceutical microsphere onto a medical device before the delivering step" (claim 15); "stent" as the medical device (claim 16); "a non-stent implant" as the medical device (claim 17); "a catheter, a wire, a cannula, and an endoscopic instrument" as the medical device (claim 19); "orally" (claim 21); "intramuscular administration" (claim 22); "said microsphere has an average diameter between 20 and 100 μm (claim 23); and "a degree of crosslinking of the crosslinked gelatin is about 60%" (claim 24).

The instant specification defines the term "microsphere" as "a pharmaceutical composition appropriately sized and shaped, comprising a bioactive agent and a biological carrier that encapsulates the bioactive agent, wherein the biological carrier is crosslinked with a corsslinking agent" (page 10, para. [0041]).

Lin teaches a biocompatible cross-linked materials such as collagen, e.g., gelatin crosslinked with genipin, suitable for use in implants, wound dressings and blood substituents (abstract; page 3, lines 6-18; page 4, lines 25-33; page 6, lines 6-10). Lin also teaches that the fabrication of such materials, particularly collagen, with or without crosslinking, into medical devices such as bioprostheses, skin and vascular grafts, and wound dressings is well known in the art (page 6, lines 11-17); that genipin-crosslinked collagenous tissues can be used in homeostasis by providing a biocompatible surface for blocking blood flow and supporting blood clotting (page 6, lines 18-22); and that determination of appropriate amount of collagen, e.g., gelatin or genipin for the desired characteristics in preparing genipin-fixed gelatin can be performed by routine experimentation (page 6, lines 23-27).

Pinchuk teaches a composition for delivery of a therapeutic agent (i.e., heparin) in polymer carrier (i.e., collagen and gelatin) in the form of medical device (e.g., catheters, guide wires, balloons, filters, stent grafts, vascular grafts, vascular patches, shunts and intraluminal paving systems) where said polymer carrier is coated on the medical device in 0.1 to 50 microns in thickness (abstract; column 2, lines 17-36 and line 43 and 53; column 7, line 17; column 12, line 20).

Tsai teaches a heparin-immobilized collagenous tissue crossed linked with genipin that is useful in preventing thrombus formation (abstract; Results and Discussions). Tsai teaches the advantage of immobilization of heparin on the genipin-fixed tissues increasing their hydrophilicity and surface tension and suppressing their mole ratio of adsorbed fibrinogen to adsorbed albumin and the amount of platelets adhered (last paragraph of page 532, column 2).

Royer and Gagnieu are being supplied as supplemental references to demonstrate routine knowledge in preparing biomaterials containing collagen or collagen derivatives such as gelatin for the production of prostheses, implants and bioencapsulation systems, e.g., microspheres and microcapsules (abstract; column 1, lines 13-22 and 36-44 of USP'579; column 4, lines 27-31 of USP'214), wherein said biomaterials can administered in various dosage forms including intramuscular or oral delivery (column 10, lines 12-18 of USP'214).

The teaching of Lin mainly differs from the claimed invention in the incorporation of heparin. To incorporate such teaching into the teaching of Lin, would have been obvious in view of Pinchuk who teaches a delivery of a therapeutic agent such as heparin in polymer carrier (i.e., gelatin and collagen) in the form of medical device and Tsai who teaches a heparin-immobilized collagenous tissue crossed linked with genipin.

Above references in combination make clear that heparin is a suitable active ingredient that can be formulated with genipin-fixed gelatin. Furthermore, above references in combination make clear that the delivering of such composition in medical devices (e.g., catheters, guide wires, balloons, filters, stent graft, vascular graft, etc...) where said composition is coated on said medical device is within the skill of the artisan.

With respect to "oral" delivery, "intramuscular" delivery, "a degree of crosslinking of the crosslinked gelatin is about 60%" and "an average diameter between 20 and 100μm" in claims 21-24 respectively, those of ordinary skill in the art would have been readily determined appropriate amounts of said component, diameters of microsphere and drug delivery system involving each of the above mentioned formulations by routine experimentation, especially in light of Royer and Gagnieu.

Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 12, 15-17, 19 and 21-24 are rejected under the judicially created doctrine of double patenting over claims 7-8, 10-16, 19-20 and 23-29 of U.S. Patent No. 6624138 B1 and further in view of Royer (USP 5783214) and Gagnieu et al. (USP 5763579).

The teaching of Royer and Gagnieu has discussed in above 35 USC 103(a) rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant method would have been obvious in light of USP'138 for following reasons.

The instant specification defines "microsphere" as "a pharmaceutical composition appropriately sized and shaped, comprising a bioactive agent and a biological carrier that

encapsulates the bioactive agent, wherein the biological carrier is crosslinked with a corsslinking agent" (page 10, para. [0041]).

Both of the instant application and the patent are directed to the administration of composition comprising drug (i.e., heparin) and biological material (i.e., gelatin), crosslinking the biological material with a crosslinking agent (i.e., genipin). Although the instant claimed invention differs from the patent mainly in (I) the specific t route of administration, namely "orally" or "intramuscularly", (ii) the specific average diameter of microsphere "between 20 and 100 μm" and (iii) the specific degree of crosslinking of the crosslinked gelatin "about 60%", such determination would have apparent to those skilled in the art, especially in light of Royer and Gagnieu.

9. In looking in continuity data, it is noted that applicant has numerous issued patent and pending applications encompassing the same or similar subject matter of the instant application. Applicant should review all subject matter considered the same or similar, and submit the appropriate Terminal Disclaimer(s). For example, 10/916170, 10/811417, USP 7101857, 10/610391, 11/180498 and 11/130787 are considered to be same or similar subject matter(s).

Conclusion

10. No Claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
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